UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,733	04/21/2006	Ian Taylor	5181	4494

35969 7590 06/09/2009

Barbara A. Shimei
Director, Patents & Licensing
Bayer HealthCare LLC - Pharmaceuticals
555 White Plains Road, Third Floor
Tarrytown, NY 10591

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
06/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,733	TAYLOR ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,15,16,18,19,21,22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 6, 15, 16, 18, 19, 21, 22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, 15, 16, 19 and 21 have been amended. Claims 2, 5, 7-14, 17, 20, 23 and 25 have been canceled. Claims 1, 3, 4, 6, 15, 16, 18, 19, 21, 22 and 24 are pending and under consideration.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of claims 1, 4, 6, 15, 18 and 19 under 35 U.S.C. 102(e) as being anticipated by Eveleigh et al (US. 2004/0121375) is maintained for reasons of record.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Eveleigh et al disclose a method comprising (a) determining the level of expression of one or more one biomarker(s) in a first biological sample taken from the patient prior to treatment with the anti-cancer agent; (b) determining the level of expression of the biomarker in at least a second biological sample taken from the patient subsequent to the initial treatment with the anti-cancer agent (claims 1, 6 and 8) Eveleigh et al disclose that samples can be obtained through biopsy (claim 5) and that cancers include solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid, and their distant metastases, as well as lymphomas, sarcomas,

and leukemias [0045 and claim 2]. Eveleigh et al disclose that the biomarkers are detected by immunohistochemical analysis [0120] and that the anti-cancer agent is a raf kinase inhibitor (claim 3). Eveleigh et al disclose that drug screening is performed by adding a test compound such as a Raf kinase inhibitor to a sample of cells and monitoring the effect (paragraph [0080]). Eveleigh et al disclose that the diagnostic assays of the invention can be carried out using antibodies to detect the protein product encoded by the marker nucleic acid sequence, such as adrenomedullin (paragraph [0130] and [0132])). Eveleigh et al disclose the detection of the marker by immunohistochemistry (paragraph [0133]).

It is noted that the recitation of a method for "monitoring the response of a patient", "providing diagnosis of cancer", "distinguishing between normal and disease tissues", "discovering novel drugs", and "selecting patients eligible for anti-cancer treatment" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Phrases such as "comparing the level of expression" are also without patentable weight as these are mental steps rather than active, tangible steps.

It is further noted that the phrase "wherein a change in the level of expression" is not given patentable weight when comparing the claims to the prior art as it simply expresses the intended result of a process step positively recited, see MPEP 2111.04.

Given that the method of the prior art comprises the same method steps as claimed in the instant invention, the claimed method is anticipated because the method will inherently be a method for identifying a compound that modulates the cell cycle. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Applicant argues that Eveleigh et al does not teach the evaluation of the protein markers, especially pERK by immunohistochemical methods. This has been considered but not found persuasive. The instant claims do not require the marker pERK. Further, Eveleigh et al does

teach the use of immunohistochemistry to measure protein markers, especially that of adrenomedullin.

Applicant argues that Eveleigh et al would benefit from exclusion under 103(c) since the subject matter and thatch of the claimed invention were at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. This has been considered but not found persuasive because the instant rejection is under 102(e), not 103(c).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, 6, 15, 16, 21, 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bacus (U.S. 2003/0045451) in view of Mantlo et al (U.S. 6,174,901) and Sivaraman et al (U.S. 6,007,991).

Claim 1 is drawn to a method comprising the steps of determining the level of expression of one or more proteins in a first biological sample taken from a patient prior to treatment with a Raf kinase inhibitor, b) determining the level of expression of the one or more proteins in at least

a second biological sample taken from the patient after treatment with the Raf kinase inhibitor, wherein the level of protein expression is assessed by immunohistochemistry

Bacus teaches a method comprising obtaining a first tissue or cell sample from an individual prior to exposure to a therapeutic agent; obtaining a second tissue or cell sample from said individual after exposure to a therapeutic agent, and comparing the amount or one or a plurality of biological makers in said first and second tissue sample (claim 1). The disclosure of a cell or tissue sample from an individual fulfills the specific embodiment of a biopsy. Bacus teaches that the amount of one or a plurality of biological markers is determined immunohistochemically (claim 6). Bacus teaches the detection of pERK as a marker [0085, line 9], thus fulfilling the requirements of claims 3, 8, 13, 16 and 21. Bacus disclose samples taken from breast and bladder [0097 and 0098]. Bacus teaches identifying responses of patients to tyrosine kinases inhibitors (paragraph [0063]). Bacus does not specifically teach tyrosine kinase inhibitors that inhibit Raf kinase.

Mantlo et al teach that Raf kinase antagonists are useful in the treatment of cancer which is mediated by Raf and Raf-inducible protein (column 3, lines 20-23). Mantlo et al teach that examples of cancers wherein Raf kinase are implicated include lung, urinary tract and stomach (column 3, lines 39-41) and that examples of cancers where upstream activators of Raf are implicated include pancreatic and breast carcinomas (column 3, lines 41-44), which fulfills the specific embodiments of claim 4. Mantlo et al teach that Raf kinase activity can be measured in vitro by the extent of substrate phosphorylation, wherein the substrate is Map kinase/ERK (column 79, lines 51-55).

Sivaraman et al teach that the level of ERK may be determined by immunohistochemical staining (column 15, lines 49-52).

It would have been prima facie obvious at the time that the claimed invention was made to substitute the screening of Raf kinase inhibitors for the screening of c-kit inhibitors in the method of Bacus . It would also have been obvious to use phosphorylated ERK as a marker for modulation of Raf kinase by using immunohistochemically detecting phosphorylated ERK. One of skill in the art would have been motivated to do so by the teachings of Mantlo et al on antagonists of Raf kinase in the treatment of cancer, and the assay of Raf kinase activity by assaying ERK phosphorylation. Further, it was obvious that ERK phosphorylation could be

detected by immunohistochemical methods as suggested by Bacus (claim 6) and taught by Sivaraman.

It is noted that the recitation of a method for "monitoring the response of a patient", "providing diagnosis of cancer", "distinguishing between normal and disease tissues", "discovering novel drugs", and "selecting patients eligible for anti-cancer treatment" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Phrases such as "comparing the level of expression" are also without patentable weight as these are mental steps rather than active, tangible steps.

It is further noted that the phrase "wherein a change in the level of expression" is not given patentable weight when comparing the claims to the prior art as it simply expresses the intended result of a process step positively recited, see MPEP 2111.04.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4, 6, 15, 18 and 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 6 00of copending Application No. 11/589,295. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '295 application anticipate the instant claims. It is noted that sorafenib is synonymous with BAY 43-9006, which is a raf-kinase inhibitor.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

All claims are rejected.

All other rejections and objections as set forth or maintained in the prior Office action are withdrawn in light of applicant's amendments.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643